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Group Art Unit: 1646

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Attorney Docket No.: 9811-013-999

For: METHODS AND COMPOUNDS FOR MODULATING NUCLEAR RECEPTOR

ACTIVITY

INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents Washington, D.C. 20231

Sir:

In accordance with the duty of disclosure provisions of 37 C.F.R. §1.56, there is hereby provided certain information which the Examiner may consider material to the examination of the subject U.S. patent application. It is requested that the Examiner make this information of record if it is deemed material to the examination of the application.

- 1. Enclosures accompanying this Information Disclosure Statement are:
 - la.

 A list of all patents, publications, applications, or other information submitted for consideration by the office.
 - 1b. A legible copy of:
 - Each U.S. patent application publication and U.S. and foreign patent;
 - Each publication or that portion which caused it to be listed on the PTO-1449;
 - For each cited pending U.S. application, the application specification including the claims, and any drawing of the application, or portion of the application which caused it to be listed on the PTO-1449 including any claims directed to that portion;
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 An English language copy of search report(s) from a counterpart foreign application or PCT International Search Report.

Explanations of relevancy (ATTACHMENT 1(d), hereto) or English language 1d. abstracts of the non-English language publications. ☑ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(b): □ Within three months of the filing date of a national application other than a continued prosecution application under §1.53(d); □ Within three months of the date of entry of the national stage as set forth in §1.491 in an international application; Before the mailing of the first Office action on the merits; Before the mailing of a first Office action after the filing of a request for continued examination under §1.114. □ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(c) after the period specified in 37 C.F.R §1.97(b), but before the mailing date of any of a final action under 37 C.F.R. §1.113, a notice of allowance under 37 C.F.R. §1.311 or an action that otherwise closes prosecution in the application. (Check either Item 3a or 3b) 3a. The Certification Statement in Item 5 below is applicable. Accordingly, no fee is required. The \$180.00 fee set forth in 37 C.F.R. §1.17(p) in accordance with 37 C.F.R. 3b. §1.97(c) is: enclosed to be charged to Pennie & Edmonds LLP Deposit Account No. 16-1150. (Item 3b to be checked if any reference known for more than 3 months) □ This Information Disclosure Statement is filed under 37 C.F.R. §1.97(d) after the period specified in 37 C.F.R. §1.97(c), but on or before the date of payment of the issue fee. The \$180.00 fee set forth in 37 C.F.R. §1.17(p) is: enclosed. to be charged to Pennie & Edmonds LLP Deposit Account No. 16-1150. The Certification Statement in Item 5 below is applicable. Certification Statement (applicable if Item 3a or Item 4 is checked)

3.

(Check either Item 5a or 5b)

In accordance with 37 C.F.R. §1.97(e)(1), it is certified that each item of information 5a. contained in this Information Disclosure Statement was first cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement.

5b. In accordance with 37 C.F.R. §1.97(e)(2), it is certified that no item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of the undersigned after making reasonable inquiry, was known by any individual designated in 37 C.F.R. §1.56(c) more than three months prior to the filing of this Information Disclosure Statement. This application is a continuation application under 37 C.F.R. §1.60 or §1.53(b) or (d). (Check appropriate Items 6a, 6b and/or 6c) 6a. A Petition to Withdraw from issue under 37 C.F.R. §1.313(b)(5) is concurrently filed herewith. Copies of publications listed on Form PTO-1449 from prior application Serial No. _ 6b. , filed on ___, of which this application claims priority under 35 U.S.C. §120, are not being submitted pursuant to 37 C.F.R. §1.98(d). 6c. Copies of the publications listed on Form PTO-1449 were not previously cited in prior application Serial No., filed on, and are provided herewith. This is a Supplemental Information Disclosure Statement. (Check either Item 7a or 7b) This Supplemental Information Disclosure Statement under 37 C.F.R. §1.97(f) 7a. supplements the Information Disclosure Statement filed on ___. A bona fide attempt was made to comply with 37 C.F.R. §1.98, but inadvertent omissions were made. These omissions have been corrected herein. Accordingly, additional time is requested so that this Supplemental Information Disclosure Statement can be considered as if properly filed on ___. □ In accordance with 37 C.F.R. §1.98, a concise explanation of what is presently understood to be the relevance of each non-English language publication is: (Check Item 8a, 8b, or 8c) 8a. satisfied because all non-English language publications were cited on the enclosed English language copy of the PCT International Search Report or the search report from a counterpart foreign application indicating the degree of relevance found by

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- 9.

 The Commissioner is authorized to charge any additional fee required or credit any overpayment for this Information Disclosure Statement and/or Petition to Pennie & Edmonds LLP Deposit Account No. 16-1150.
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 No admission is made that the information cited in this Statement is, or is considered to be, material to patentability nor a representation that a search has been made (other than a search report of a foreign counterpart application or PCT International Search Report if submitted herewith). 37 C.F.R. §§1.97(g) and (h).

Respectfully submitted,

Date: January 28, 2003

Richard G. A. Bone

(Reg. No.)

Limited Recognition Under 37 C.F.R. § 10.9(b)

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for Samuel B. Abrams

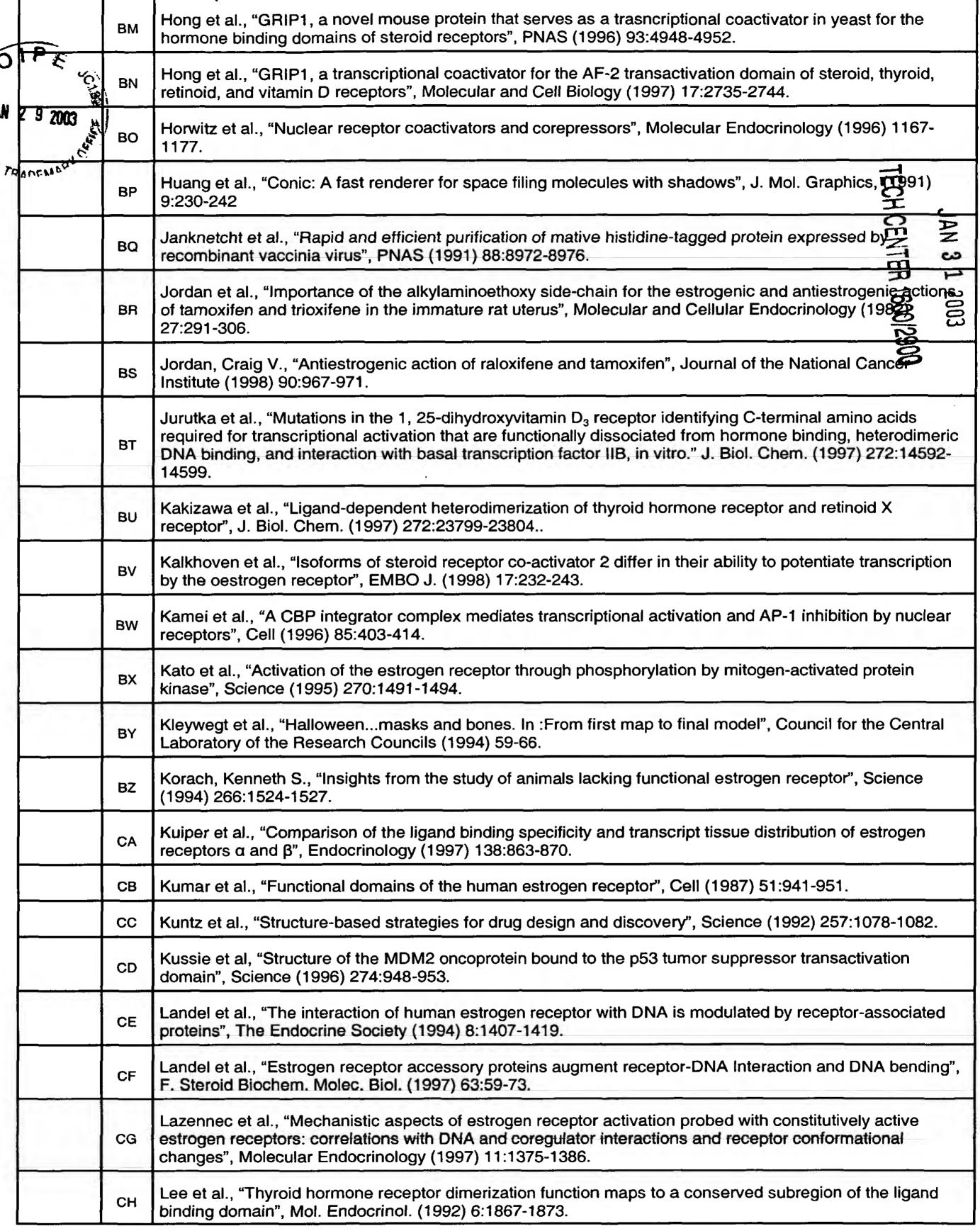
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| | AC | WO 92/00091 | 1/09/92 | PCT | | | | | |
| | AD | WO 93/06121 | 4/01/93 | PCT | | | | | |
| | AE | WO 94/28028 | 12/08/94 | PCT | | | | | |
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| , | <u></u> | OTHER RE | FERENCES (In | ncluding Author, Title | e, Date, Pertinent Pages, Etc.) | | | | |
| | AG | Adams et al., "Cross-validated maximum likelihood enhances crystallographic simulated annealing refinement", PNAS (1997) 94:5018-5023. | | | | | | | |
| | АН | Anzick et al., "AIB1, a steroid receptor coactivator amplified in breast and ovarian cancer", Science (1997) 277:965-968 | | | | | | | |
| | Al | Apriletti et al., "Expression of the rat α1 thyroid hormone receptor ligand binding domain in Escheria coli and the use of a ligand-induced conformation change as a method fo its purification to homogeneity", Protein Expr. Purif., (1995) 6:363-370. | | | | | | | |
| | AJ | Beato et al., "Steroid hormone receptors: many actors in search of a plot", Cell (1995) 83:851-857. | | | | | | | |
| | AK | Berry et al., "Role of the two activating domains of the oestrogen receptor in the cell type and promoter context dependent agonistic activity of the anti-oestrogen 4-hydroxytamoxifen", the EMBO J. (1990) 9:2811-2818 | | | | | | | |
| | AL | Bourguet et al., "Cryst Nature (1995) 375:377 | | f the ligand-bindi | ng domain fo the human nu | uclear re | eceptor RX | R-α", | |
| | АМ | Brzozowski et al., "Mo 389:753-758. | lecular basis | of agonism and | antagonism in the oestroge | n recep | tor", Nature | e (199 | 7) |
| | AN | Chang et al., "A thyroid PNAS (1997) 94:9040 | | ceptor coactivato | or negatively regulated by the | he retino | oblastoma | protei | n", |
| | AO | | | | novel histone acetyltransf p300", Cell (1997) 90:569- | | nd forms a | | |

| PK | AP | Cohen et al., "Molecular modeling software and methods for medicinal chemistry", J. Med. Chem. (1990) 33:883-894. |
|---------|----|--|
| yC139 | AQ | Collaborative Computational Project, Number 4 "The CCP4 Suite: Programs for Protein Crystallography", Acta Cryst. (1994) D50 760-763. |
| May Car | AR | Collingwood et al., "A natural transactivation mutation in the thyroid hormone β receptor: Impaced interaction with putative transcriptional mediators", PNAS (1997) 94:248-253. |
| M. J | AS | Danielian et al., "Identification of a conserved region required for hormone dependent transcriptional activation by steroid hormone receptors", EMBO J. (1992) 11:1025-1033. |
| | АТ | Darimont et al., "Structure and specificity of nuclear receptor-coactivaor interactions", Genes E Development (1998) 12:3343-3356. |
| | AU | Desjarlais et al., "Using shape complementarily as an initial screen in designing ligands for a perpention of binding site of known three-dimensional structure", J. Med. Chem. (1988) 31:722-729. |
| | AV | Ding et al., "Nuclear receptor-binding sites of coactivators glucocorticoid receptor interacting protein 1 (GRIP1) and steroid receptor coactivator 1 (SRC-1): multiple motifs with different binding specificities", Molecular Endocrinology (19980 12:302-313. |
| | AW | Douarin et al., "A possible involvement of TIF1 α and TIF1 β in the epigenetic control of transcription by nuclear receptors", (1996) 15:6701-6715. |
| | AX | Eng et al., "Probing the structure and function of the estrogen receptor ligand binding domain by analysis of mutants with altered transactivation characteristics", Molecular and Cellular Biology (1997) 17:4644-4653. |
| | AY | Esnouf et al., "An extensively modified version of MolScript that includes greatly enhanced coloring capabilities", Journal of Molecular Graphics and Modeling (1997), 15:132-134. |
| | AZ | Farmer et al., "Drug design", Ariens, E.J. ed. (1980) 10:119-143. Academic Press NY. |
| | ВА | Feng et al., "Hormone-dependent coactivator binding to a hydrophobic cleft on nuclear receptors", Science (1998) 280:1747-1749. |
| | ВВ | Furey et al., "Phases' - A program package for the processing and analysis of diffraction data from macromolecules," Am. Crust. Assoc. Mtg. Abstr. (1990) 18:73. |
| | вс | Glass et al., "Nuclear receptor coactivators" Current Opinion in Cell Biology (1997) 9:222-232. |
| | BD | Gradishar et al., "Clinical potential of new antiestrogens", (1997) 15:840-852 |
| | BE | Grainer et al., "Tamoxifen: Teaching an old drug new tricks?" Nature Medicine (1996) 2:381-385. |
| | BF | Greene et al., "Purification of T47D human progesterone receptor and immunochemical characterization with monoclonal antibodies", Molecular Endocrinology (1988) 2:714-726. |
| | BG | Greene et al., "Monoclonal antibodies to human estrogen receptor" PNAS (1980) 77:5115-5119 |
| | ВН | Grese et al., "Molecular determinants of tissue selectivity in estrogen receptor modulators", PNAS (1997) 94:14105-14110. |
| | B≀ | Hanstein et al., "p300 is a component of an estrogen receptor coactivator complex", PNAS (1996) 93:11540-11545. |
| | BJ | Heery et al., "A signature motif in transcriptional co-activators mediates binding to nuclear receptors", Nature (1997) 387:733-736. |
| | вк | Hegy et al., "Carboxymethylation of the human estrogen receptor ligand binding domain estradiol complex: HPLC/ESMS peptide mapping shows that cysteine 447 does not react with iodoacetic acid", Steroids (1996) 61:367-373. |
| | BL | Henttu et al., "AF-2 activity and recruitment of steroid receptor coactivator 1 to the estrogen receptor depend on a lysine residue conserved in nuclear receptors", Molecular and Cellular Biology (1997) 17:1832-1839 |



| CI F | Li et al., "RAC3 a steroid nuclear receptor associated coactivator that is related to SRC-1 and TIF2", PNAS (1997) 94:8479-8484. |
|-------------|--|
| a 2003 2 CJ | Lin et al., "A conformation switch in nuclear hormone receptors is involved in coupling hormone binding to a corepressor release", Mol. Cell. Biol. (1997) 17:6131-6138. |
| CK CK | Masuyama et al., "Evidence for ligand dependent intramolecular folding of the AF-2 domain in vitamin D receptor activated transcription and coactivator interaction", Mol. Endocrinol. (1997) 11:1507-1573. |
| CL | Meng et al., "Automated docking with grid based energy evaluation", J. Computational Chem. (1992) 2 13:505-524. |
| СМ | Merritt et al., "Raster 3D Version 2.0 A Program for Photorealistic Molecular Graphics", Acta Cryst. (1994) D50 869-873. |
| CN | Moras et al., "The nuclear receptor ligand binding domain: structure and function", Current Opinios n Cell Biology (1998) 10:384-391. |
| со | Mueller et al., "Complex heterocyclic structures a challenge for computer assisted molecular modeling" Bull. Soc. Chim. Belg. (1988) 97:655-667 |
| СР | Murshudov et al., "Refinement of macromolecular structures by the maximum likelihood method", Acta Cryst (1997) D53 240-255. |
| cq | Navia et al., "Use of structural information in drug design", Curr. Opin. Struct. Biol. (1992) 2:202-210. |
| CR | Nolte et al., "Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-γ" Nature (1998) 395:137-143. |
| cs | Norman et al., "The rat growth hormone gene contains multiple thyroid response elements", J. Biol. Chem. (1989) 264:12063-12073. |
| СТ | Norris et al., "Enhancement of estrogen receptor transcriptional activity by the coactivator GRIP-1 highlights the role of activation function 2 in determining estrogen receptor pharmacology", The Journal of Biological Chemistry (1998) 273:6679-6688. |
| CU | O'donnell et al., "Thyroid hormone receptor mutations that interfere with transcriptional activation also interfere with receptor interaction with a nuclear protein", Molecular Endocrinology (1991) 5:94-99. |
| cv | Onate et al., "Sequence and characterization of a coactivator for the steroid hormone receptor superfamily", Science (1995) 270:1354-1357. |
| cw | Otwinowski et al., "Processing of X-Ray diffraction data collected in oscillation mode", Methods in Enzymology (1997) 276:307-326. |
| СХ | Radhakrishnan et al., "Solution structure of the KIX domain of the CBP bound to the transactivation domain of CREB: A model for activator Coactivator interactions", Cell (1997) 91:741-752. |
| CY | Renaud et al., "Crystal structure of the RAR-γ ligand-binding domain bound to all-trans retinoic acid", Nature (1995) 378:681-689. |
| cz | Robertson et al., "Antiestrogen basicity-activity relationships: A comparison of the estrogen receptor binding and antuterotrophic potencies of several analogues of (Z)-1,2-Diphenyl-1-[4[2-(dimethylamino)ethoxy]phenyl]-1-butene (tamoxifen, nolvadex) having altered basicity", J. Med. Chem. (1982) 25:167-171. |
| DA | Saatcioglu et al., "Mutations in the conserved C-terminal sequence in thyroid hormone receptor dissociate hormone-dependent activation from interference with AP1-activity", Mol. Cell. Biol. (1997) 17:4687-4695. |
| DB | Sadovsky et al., "Transcriptional activators differ in their responses to overexpression of the TATA-Box binding protein", Molecular and Cellular Biology (1995) 15:1554-1563. |
| DC | Seielstad et al., "Analysis of the structural core of the human estrogen receptor ligand binding domain by selective proteolysis/mass spectrometric analysis" Biochemistry (1995) 34:12605-12615. |
| DD | Seielstad et al., "Molecular characterization by mass spectrometry of the human estrogen receptor ligand- binding domain expressed in Escherichia coli" Molecular Endocrinology, (1995) 9:647-658. |

| DE | Shiau et al., "Activation of the human estrogen receptor by estrogenic and antiestrogenic compounds in Saccharomyces cerevisiae, a positive selection system", Gene (1996) 179:205-210. |
|-------------|---|
| DF C 38 | Shiau et al., "The structural basis of estrogen receptor/coactivator recognition and the antagonism of this interaction by Tamoxifen", Cell (1998) 95:927-937. |
| Z 9 2003 DG | Shibata et al., "Role of co-activators and co-repressors in the mechanism of steroid/thyroid receptor action Recent Prog. Horm. Res. (1997) 52:141-164. |
| ANENDO | Smigel et al., "Breast cancer prevention trial shows major benefit, some risk", Journal of the National Cancer Institute (1998) 90:647-648 |
| DI | Smith et al., "Estrogen resistance caused by a mutation in the estrogen receptor gene in a man". The New England Journal of Medicine (1994) 331:1056-1061. |
| DJ | Spencer et al., "Steroid receptor coactivator-1 is a histone acetyltransferase", Nature (1997) 389:194-198. |
| DK | Tagami et al., "Nuclear receptor corepressors activate rather than suppress basal transcription of genes that are negatively regulated by thyroid hormone", Molecular and Cellular Biology (1997) 17:2642-2648. |
| DL | Takeshita et al., "Molecular cloning and properties of a full length putative thyroid hormone receptor coactivator", Endocrinology (1996) 137:3594-3597. |
| DM | Tanenbaum et al., "Crystallographic comparison of the estrogen and progesterone receptors ligand bindin domains", PNAS (1998) 95:5998-6003. |
| DN | Tora et al., "The cloned human oestrogen receptor contains a mutation which alters its hormone binding properties", the EMBO J. (1989) 8:1981-1986. |
| DC | Torchia et al., "The transcriptional co-activator p/CIP binds CBP and mediates nuclear-receptor function", Nature (1997) 387:677-684. |
| DF | Tsai et al., "Molecular mechanisms of action of steroid/thyroid receptor superfamily members", Annu. Rev Biochem. (1994) 63:451-86. |
| DC | Uesugi et al., "Induced α-helix in the VP 16 activation domain upon binding to a human TAF" Science, (1996) 277:1310-1313. |
| DF | Verlinde et al., "Structure-based drug design: Progress, results and challenges", Structure (1994) 2:577-587. |
| DS | Voegel et al., "The coactivator TIF2 contains three nuclear receptor-binding motifs and mediates transactivation through CBP binding-dependent and independent pathways", the EMBO J (1998) 17:507-519. |
| DT | Voegel et al., "TIF2 a 160kDa transcriptional mediator for the ligand-dependent activation function AF-2 or nuclear receptors", the EMBO J (1996) 15:3667-3675. |
| DU | Wagner et al., "A structural role for hormone in the thyroid hormone receptor", Nature (1995) 378:690-697 |
| DV | Wallace et al., "LIGPLOT: a program to generate schematic diagrams of protein ligand interactions", Protein Engineering (1995) 8:127-134. |
| DV | Webb et al., "Tamoxifen activation of the estrogen receptor / AP-1 Pathway: Potential origin for the cell-specific estrogen-like effects of antiestrogens", Molecular Endocrinology., (1995) 9:443-456. |
| DX | White et al., "Ligand independent activation of the oestrogen receptor by mutation of a conserved tyrosine the EMBO J. (1997) 16:1427-1435. |
| DY | Whitefield et al., A highly conserved region in the hormone binding domain of the human vitamin D recept contains residues vital for heterodimerization with retinoid X receptor and for transcriptional activation", Molecular Endocrinology (1995) 9:1166-1179. |
| DZ | Williams et al., "Atomic structure of progesterone complexed with its receptor", Nature (1998) 393:392-39 |
| EA | Wrenn et al., "Structure-function analysis of the hormone binding domain of the human estrogen receptor by region-specific mutagenesis and phenotypic screening in yeast", The Journal of Biochemistry (1993) 268:24089-24098. |

| | EB | Wurtz et al., "A canonical structure for the ligand-binding domain of nuclear receptors", Nature and Structural Biology (1996) 3:87-94 | | | |
|------------|-----------|--|--|--|--|
| 1017 | 1013 | Xu et al., "Partial hormone resistance in mice with disruption of the steroid receptor coactivator-1 (SRC-1) gene", Science (1998) 279:1922-1925. | | | |
| 2 9 2003 | U.ED | Zhu et al., "The different hormone-dependent transcriptional activation of thyroid hormone receptor isoforms is mediated by interplay of their domains", J. Biol. Chem. (1997) 272:9048-9054. | | | |
| A A DE MAR | EE | (X-PLOR Resources) Http://xplor.csb.yale.edu/explor-info/ Last accessed on 11/16/98 | | | |
| | EF | Grasp Manual Page http://honiglab.cpmc.columbia.edu/grasp/grasp_man.html Last accessed on 11/16/98 | | | |
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